

ORIGINAL RESEARCH

Hyaluronic acid treatment of facial fat atrophy in HIV-positive patients

H Bugge,[1] A Negaard,[2] L Skeie[3] and B Bergersen[4]

[1]*Department of Plastic Surgery,* [2]*Department of Radiology,* [3]*Department of Infectious Diseases, Ulleval University Hospital, N-0407 Oslo,* [4]*Department of Infectious Diseases, Aker University Hospital, 0514 Oslo, Norway*

Objectives

Facial lipoatrophy can be devastating for HIV-infected patients, with negative effects on self-esteem. In this study, we treated facial fat atrophy in the nasogenian area with hyaluronic acid (Restylane SubQ; Q-Med AB, Uppsala, Sweden).

Methods

Twenty patients were included in the study. Treatment effects were evaluated at baseline, and at weeks 6, 24 and 52 using ultrasound, the Global Aesthetic Improvement Scale, the Visual Analogue Scale and the Rosenberg Self-Esteem Scale.

Results

Mean ($\pm$ standard deviation) total cutaneous thickness increased from 6 ± 1 mm at baseline to 15 ± 3 mm at week 6 ($P < 0.001$), and declined to 10 ± 2 mm at week 52 ($P < 0.001$ vs baseline). The response rate (total cutaneous thickness > 10 mm) was 100% at week 6, 85% at week 24 and 60% at week 52. At week 6, all of the patients classified their facial appearance as very much improved or moderately improved. They also reported increased satisfaction with their facial appearance and had higher self-esteem scores. At week 52, 15 of 19 patients still classified their facial appearance as very much improved or moderately improved, although the mean total cutaneous thickness had gradually declined.

Conclusions

Our results indicate that Restylane SubQ is a useful and well-tolerated dermal filler for treating HIV-positive patients with facial lipoatrophy.

Keywords: antiretroviral therapy, facial fat atrophy, HIV, hyaluronic acid, SubQ

Received: 19 February 2007, accepted 19 June 2007

Introduction

Facial fat atrophy is a known adverse event in HIV-positive patients on antiretroviral therapy. Facial fat atrophy can negatively impact patients' quality of life and may contribute to a reduction in patient adherence to antiretroviral therapy [1]. It has been reported that affected patients encounter stigmatization as a result of facial lipoatrophy which can in turn erode self-esteem [2]. Treatment strategies include switching antiretroviral regimens, prescription of medication, insertion of surgical implants and injection of dermal fillers.

Correspondence: Dr Bente Bergersen, Department of Infectious Diseases, Aker University Hospital, 0514 Oslo, Norway. Tel: + 47 22 894739; fax: + 47 22 894008; e-mail: b.m.bergensen@medisin.uio.no

Switching away from thymidine analogues has been shown to have only a modest effect on the recovery of subcutaneous fat mass. A follow-up study of the Oslo HIV Cohort Study 2000 found that facial atrophy was less reversible than fat atrophy of the extremities [3]. Although pioglitazone (a new antidiabetic drug) [4] has recently been shown to have an effect on limb lipoatrophy in HIV-infected patients, the specific effect of pioglitazone and similar drugs on facial lipoatrophy is not documented.

Injection of soft-tissue fillers appears to be the simplest way to correct facial lipoatrophy. There are numerous soft-tissue fillers, and they can be divided into two main categories: nonpermanent and permanent fillers. Nonpermanent fillers are also known as temporary or reabsorbable fillers and include polylactic acid, collagen, and calcium hydroxyapatite. Injectable silicone, polymethylmethacrylate

microspheres and polyacrylamide gel are permanent fillers. Injected autologous fat can be nonpermanent or permanent. Injectable hyaluronic acid derivatives are the most commonly used reabsorbable dermal fillers for soft-tissue augmentation today [5], and have replaced collagen as the standard injection material [6]. However, there are no long-term studies on the treatment of HIV-related lipoatrophy with hyaluronic acid.

Hyaluronic acid products have been demonstrated to have a good safety profile, and few complications have been reported after the product was improved [7,8]. The hyaluronic acid product Restylane (Q-Med AB, Uppsala, Sweden) is produced from a hyaluronic acid preparation obtained by bacterial fermentation. The use of a nonanimal source is thought to reduce the likelihood of antigenic contamination and subsequent hypersensitivity reactions. Restylane received approval by the Food and Drug Administration in 2003 [7]. The new Restylane product Restylane SubQ was introduced in September 2004. The main difference between Restylane SubQ and other Restylane products is the size of the gel particles and the intended level of injection. Restylane SubQ has fewer gel particles (1000 gel particles/mL) and thus larger droplets than other Restylane products, and is therefore more viscous. SubQ can therefore be injected in larger amounts and into deeper skin layers [9].

The main aim of this study was to evaluate the efficacy, safety and durability of the new Restylane product SubQ in the correction of facial lipoatrophy in HIV-infected patients.

Methods

Study population

The patients were primarily recruited from the Oslo HIV Cohort 2000, a study in which the body composition changes and cardiovascular risk factors of 308 ambulatory HIV-positive patients have been evaluated [3,10]. In May 2004, a letter of invitation was sent to all Oslo HIV Cohort patients who were still alive and had a known address; in total, 278 patients. Information about the lipoatrophy treatment study was also sent to patient organizations and HIV health providers in Oslo, Bergen, Trondheim and Tromsoe. HIV-infected patients older than 18 years of age with severe nasogenian atrophy (readily noticeable to a casual observer) that had not previously been treated with injectable fillers were considered eligible for inclusion. The study protocol was evaluated by the Regional Committee for Medical Research Ethics and approved by the Norwegian Data Inspectorate. This study has been conducted in full accordance with the World Medical Association Declaration of Helsinki.

Study treatment

The treatment was given in one or two sessions only. At baseline, the patients received an injection of approximately 1.5–2.0 mL hyaluronic acid in each cheek in the nasogenian area. A touch-up treatment was offered at week 4, and 15 of 20 patients had an injection of approximately 1.0 mL in each cheek at week 4. No more touch-up treatments were given in the following year.

All the injections were performed by the same plastic surgeon at the out-patient clinic of the Department of Plastic Surgery. The skin area was pen-marked with the patient in an upright position before the patient lay down for treatment. Under local anaesthesia, a sharp 18-gauge cannula was used to perforate the skin laterally, just below the cheek bone. A blunt-tipped cannula with side-exit (1.2×70 mm; 18 gauge) was then inserted downwards and subcutaneously on each side, to make a tunnel. The tunnel was then filled with Restylane SubQ gel while the cannula was being retracted. Filling with Restylane SubQ was carried out using a fanning injection technique (12–16 tunnelations) (Fig. 1). At the end of each treatment, the cheeks were gently massaged in order to shape the filler material to achieve optimal contour.

Follow-up

Patients were evaluated using digital photography, ultrasound and clinical examinations, which included the use of scales to measure satisfaction with facial appearance and self-esteem at baseline (preoperatively), and at weeks 6, 24

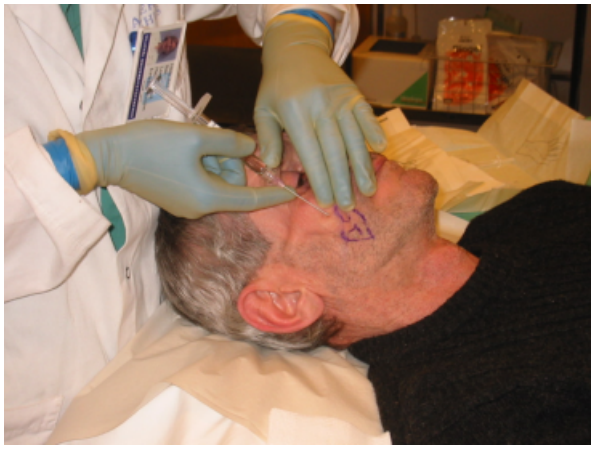

Fig. 1 The injection technique.

and 52. Following each treatment and at weeks 24 and 52, patients were asked to complete a questionnaire about the following adverse events: swelling, tenderness, pain, redness, lumps and fever. Patients were assessed using the Global Aesthetic Improvement Scale at weeks 6, 24 and 52.

Radiological assessment

Standardized ultrasonography was used to measure the total cutaneous thickness (epidermal, dermal and subcutaneous thickness) in the nasogenian area, which is located below the malar bone in front of the masseter muscle. The examination was conducted by a radiologist, using a scanner (Acuson-Siemens Sequoia 512; Siemens Medical Solutions, Mountainview, CA) equipped with a 14-MHz linear array transducer. A large amount of acoustic coupling gel was used and the scanning was performed with minimal pressure. Four measurements were made from each nasogenian area and a mean value (right + left cheek)/2 was calculated at each visit. All the ultrasonographic examinations were recorded. A treatment responder was defined as a patient with a total cutaneous thickness > 10 mm.

Clinical evaluation

Global Aesthetic Improvement Scale

The Global Aesthetic Improvement Scale [11] is a five-grade subjective test for efficacy analysis. The physician and patient independently compared the preoperative photograph with the treated face and answered the question: 'How would you describe the degree of improvement?' Possible responses were (1) very much improved, (2) moderately improved, (3) somewhat improved, (4) no change or (5) worse.

Visual Analogue Scale

Patients were asked to record how satisfied they were with their facial appearance in relation to their lipoatrophy on a 10-cm visual analogue scale from 'not satisfied at all' to 'completely satisfied'. The results were translated to numbers from 0 to 100 by measuring in millimetres from the beginning of the scale.

Rosenberg Self-Esteem Scale

Patients were also asked to complete a questionnaire to assess self-esteem at each visit. The Rosenberg Self-Esteem Scale [12] is a widely-used self-esteem measure in social science research and was used to capture information about possible changes in patients' self-esteem following treatment with hyaluronic acid. The scale consists of 10 statements dealing with general feelings about oneself. For example, 'On the whole, I am satisfied with myself.' Responses were given on a seven-point scale from 0 (strongly disagree) to 6 (strongly agree) and scores ranged from 0 (low self-esteem) to 6 (high self-esteem).

Statistical analyses

Related samples tests were used to compare values obtained at the first and second visits: the Wilcoxon signed-rank test was used for continuous variables and the McNemar test for binary variables. The level of significance used was 5%. Results are presented as mean $\pm$ standard deviation, unless otherwise stated.

Results

Twenty-seven patients applied to take part in the study. Six patients were not included because of minimal facial changes, and one was excluded because of previous injections of hyaluronic acid. Twenty patients, one female and 19 male, were enrolled between September 2004 and April 2005 and are included in the study analysis. At baseline, the patients were 49 ± 7 years old and their mean weight was 74.7 ± 10.0 kg. They had a long history of HIV infection; the duration from the first positive test was 13.6 years (minimum 8.5 and maximum 20.0 years), and the mean time on antiretroviral therapy was 10.0 years (minimum 6.9 and maximum 15.6 years). All but one patient had been on stavudine (mean time on stavudine 40 ± 27 months) and 17 had stopped taking stavudine at least 1 year before inclusion. Details about the use of zidovudine were not included. The patients' HIV infection was well controlled; the mean CD4 count was 520 ± 320 cells/μL and 14 (70%) had HIV RNA < 50 copies/mL.

Radiological assessment

Mean ($\pm$ standard deviation) total cutaneous thickness increased from 6 ± 1 mm at baseline to 15 ± 3 mm at week 6 ($P < 0.001$), and declined to 10 ± 2 mm at week 52 ($P < 0.001$ vs baseline) (Fig. 2). The response rate, defined as total cutaneous thickness > 10 mm, was 100% at week 6. In the intention-to-treat analysis, the response rate was 85% at week 24 (17/20; one patient missing) and 60% at week 52 (12/20; two patients missing).

Clinical evaluation

Global Aesthetic Improvement Scale

When evaluating the effect of treatment using the Global Aesthetic Improvement Scale at week 6, all of the patients

classified their facial appearance as very much or moderately improved (Table 1). At week 52, 15 of the 19 remaining patients classified their facial appearance as very much improved or moderately improved. Thirteen patients wanted touch-up treatment at week 52.

Visual Analogue Scale and Rosenberg Self-Esteem Scale

At 6 weeks, patient visual analogue assessments and self-esteem scores had increased significantly from baseline (Table 2). Significant improvements on visual analogue and self-esteem scores, although somewhat reduced, persisted through to week 52.

Adverse events

There were no serious adverse effects and no treatment interruptions because of side effects. Most patients experienced some local swelling and tenderness on the first 1–3 days following treatment and some had local redness (Table 3). Eight of the patients had palpable lumps after one or two treatments. Some of these were visible and in three of the patients the lumps were still present at week 52. One lump was localized at the injection site and was movable (Fig. 5a). Another patient reported fever, redness, swelling and vesicles on his right cheek 2–3 days after treatment. He recognized the vesicles as recurrent herpes zoster and self-treated with acyclovir. Following the touch-up treatment at week 4, he had a similar reaction (this time without vesicles) on his left cheek (Fig. 3). These changes were evaluated by the physician as reactive and noninfectious and resolved after 2–3 days without medical treatment.

Table 1 The Global Aesthetic Improvement Scale, showing patients' satisfaction with their facial appearance when compared with a preoperative photograph 6, 24 and 52 weeks after treatment

	Number of patients		
	6 weeks	24 weeks	52 weeks
Very much improved	14/20	13/20	5/19
Moderately improved	6/20	5/20	10/19
Somewhat improved	0	2/20	2/19
No change	0	0	2/19
Worse	0	0	0

Table 2 The Visual Analogue Scale and Rosenberg Self-Esteem Test

	Score (mean ± standard deviation)		
	Baseline ($n = 20$)	6 weeks ($n = 20$)	52 weeks ($n = 20$)
Visual Analogue Scale	39 ± 25	80 ± 15*	71 ± 16*
Rosenberg Self-Esteem Scale	41 ± 10	47 ± 8*	44 ± 9*

*$P < 0.05$ compared with baseline.

Table 3 Adverse events after hyaluronic acid injections in 20 HIV-positive patients with facial lipoatrophy

	Number of patients	
	Baseline treatment ($n = 20$)	Touch-up treatment, week 4 ($n = 15$)
Swelling	13	7
Tenderness	12	10
Pain	3	2
Redness	5	2
Fever	1	1

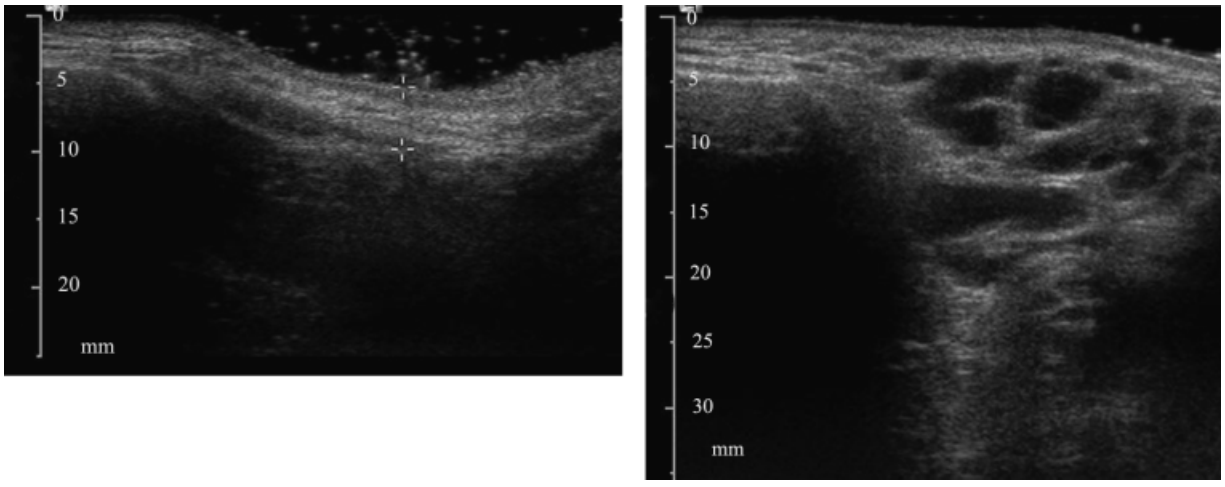

Fig. 2 Total cutaneous thickness at baseline and 6 weeks after hyaluronic injection.

Cost of treatment

Each patient required approximately 6 mL of Restylane SubQ in the baseline treatment including touch-up. Thirteen patients had a refill treatment at week 52 which was similar to the baseline treatment (about 6 mL including touch-up at week 56). With the full price for 1 mL of Restylane SubQ being €160 (including taxes and blunt-tip application cannulas; no discount), the yearly cost of filling material (approximately 6 mL) can be estimated to be approximately €950.

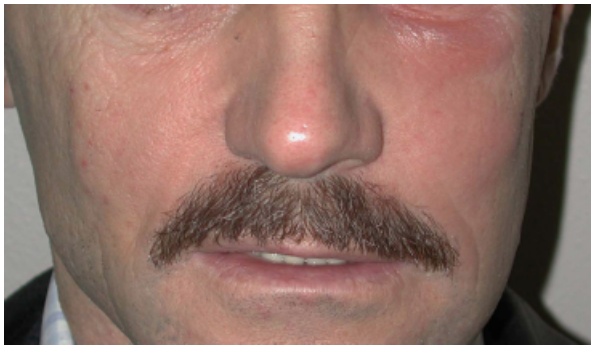

Fig. 3 Reactive reaction 2–3 days after injection with hyaluronic acid.

Discussion

In our study using the temporary dermal filler Restylane SubQ, mean total cutaneous thickness increased from 6 ± 1 mm at baseline to 15 ± 3 mm at week 6 and declined to 10 ± 2 mm at week 52. Response rate, defined as total cutaneous thickness > 10 mm, was 100% at week 6, 85% at week 24 and 60% at week 52 (intention-to-treat analysis). Global Aesthetic Improvement Scale results showed improvement for about 90% of patients at week 52 despite the fact that all patients had a reduction in the degree of correction compared with week 6. Similarly, a significant increase in self-esteem scores and visual analogue scores, measuring patient satisfaction with their appearance, was found between baseline and week 52.

The major disadvantage of temporary fillers is the need for ongoing reapplication. However, in contrast to a previous study which reported that the hyaluronic acid product Restylane Perlane lasted for 3–6 months [13], we found that with Restylane SubQ 60% of the patients had

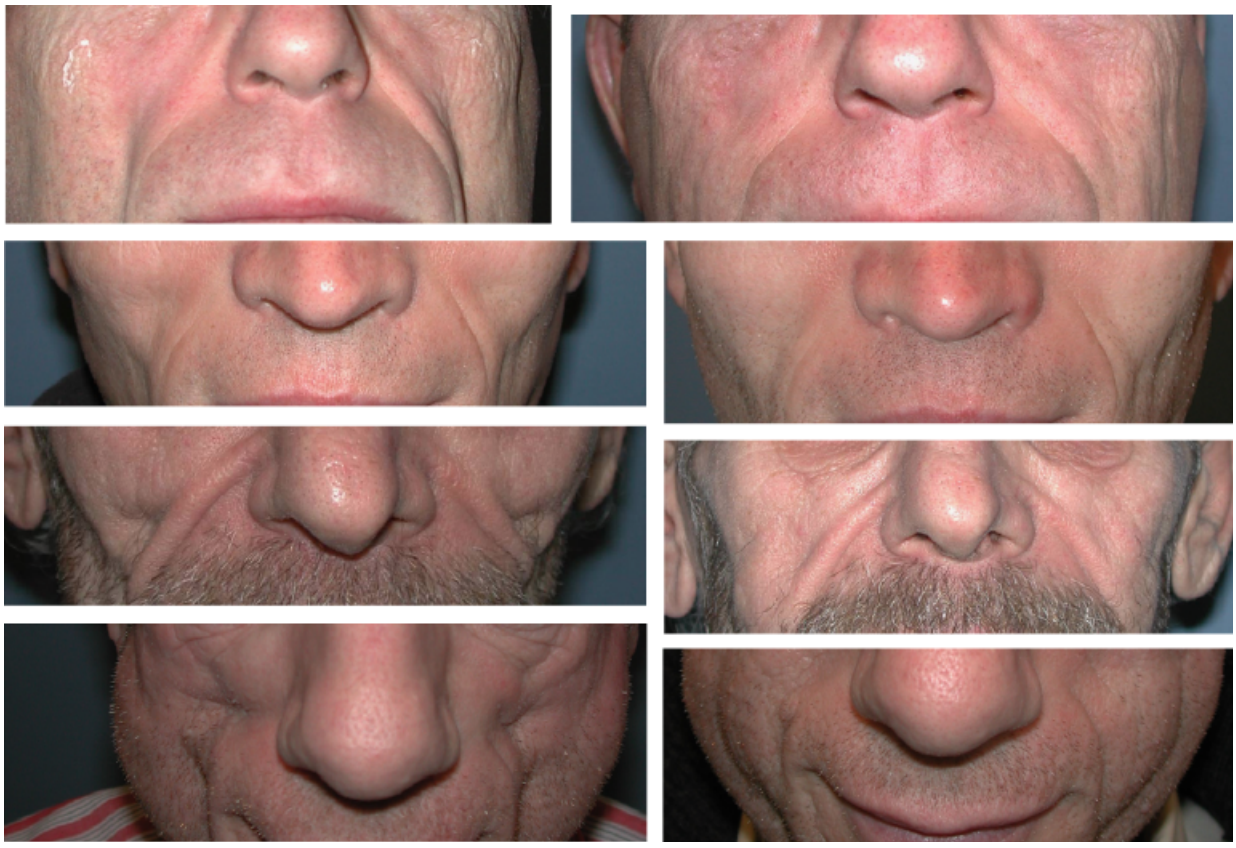

Fig. 4 Clinical change following hyaluronic acid injections in four patients at baseline and week 6.

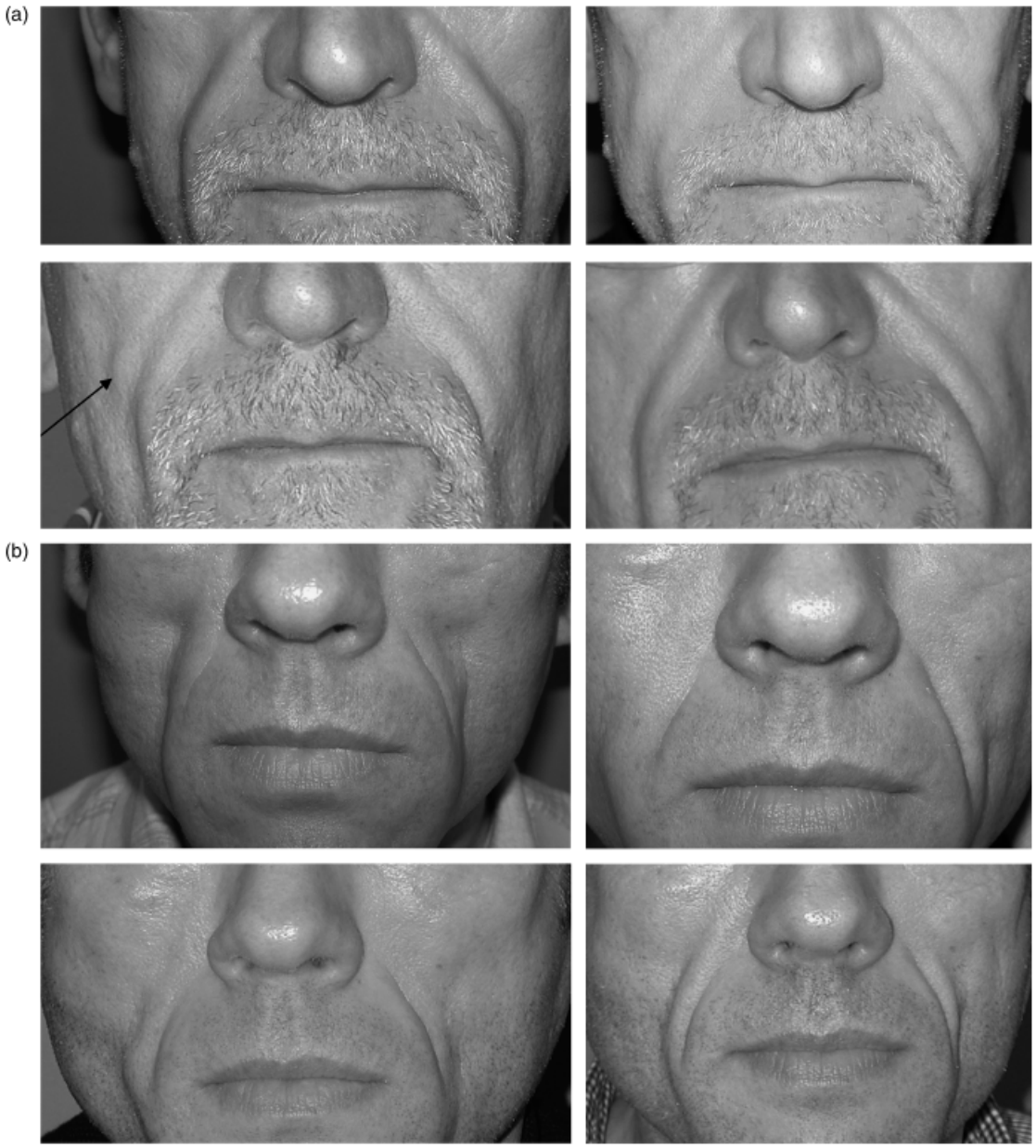

Fig. 5 (a) Clinical change following hyaluronic acid injections in one patient at baseline, weeks 6, 24 and 52. Notice the small lump at week 24 (arrow). (b) Clinical change following hyaluronic acid injections in one patient at baseline, weeks 6, 24 and 52.

total cutaneous thickness >10 mm 52 weeks after the baseline treatment. No additional touch-up treatments were given between weeks 4 and 52. These results suggest that yearly reapplication of Restylane SubQ (in one or two sessions, 2–3 weeks apart) should be sufficient. Polylactic acid has probably been the material most often used in the treatment of HIV-related facial fat atrophy. The effect of polylactic acid has been reported to persist even longer, but this product needs multiple treatment sessions in order to obtain the desired effect [1,14]. It may take several months for the treatment results with polylactic acid to stabilize and for the full magnitude of the facial augmentation to become apparent [15]. In the study by Valantin *et al.* [14] the proportion of patients with total cutaneous thickness >10 mm was 19% at week 6, 41% at week 24, 61% at week 48, 52% at week 72 and 43% at week 96. In this study, most patients received four or five sets of injections of polylactic acid every 2 weeks.

In our study, adverse events were confined to local injection-site reactions arising from the implant or the injection procedure, and the majority of these were mild. One patient had a facial swelling including the eyelids at the first and second injections. Exactly the same reactions to hyaluronic acid have not been described in detail previously, but 'redness and swelling' are frequently reported. Our patient was re-treated at week 52 without any reactions, and thus an allergic reaction seems unlikely.

Eight of the patients had palpable lumps after one or two treatments. Similar lumps have not been reported in other hyaluronic acid studies. However, the producers of Restylane SubQ were aware of this tendency to lump formation and advised against injecting more than 2 mL per treatment. It is also important that the gel is injected in small aliquots spread into the area to be augmented to avoid lump formation. This is, of course, particularly difficult in patients in whom lack of subcutaneous fat is a problem.

Polylactic acid can cause foreign-body granuloma reactions [6,15]. Case reports have also described granulomas and abscess-like nodule formations following hyaluronic acid treatment; however, most of the patients in these reports received facial injections before 2000 [5,16–18]. A possible explanation for this is that after 2000 the amount of protein in hyaluronic acid was decreased [8]. No such changes were observed in our study at week 52; however, we acknowledge that the number of subjects may be insufficient to detect such rare complications.

In addition to hyaluronic acid and polylactic acid, fat transplantation [19] has also been used in the treatment of HIV-associated facial lipoatrophy. An important limitation to the use of fat transplantation in this patient group is the general lack of subcutaneous fat tissue in these patients, which leads to problems in obtaining enough donor fat [19]. Fat transplantation is a more complicated and time-consuming procedure than injection of synthetic fillers. In addition, some cases of disfiguring fat graft hypertrophy have been described [20]. Permanent fillers such as silicone may be ideal fillers when correctly placed, and no long-term side effects occur; the material is permanent and no reapplication is needed. However, there are some well-documented side effects of permanent fillers [21]. Granuloma formation typically occurs a couple of years after treatment [22]. In cases of infection, the permanent material must be extracted, and this may be difficult if it has been injected into soft tissue. Migration of permanent implants has also been described [23].

The need for treatment of facial lipoatrophy in Norway is not very great. There are roughly 2500 people living with HIV in Norway, of whom about 5% are in need of treatment, and this number is likely to decrease, as current antiretroviral regimens do not appear to cause lipoatrophy to the same extent as previous regimens [24].

Conclusion

This is the first study using Restylane SubQ to treat HIV-related facial lipoatrophy, and our results show that hyaluronic acid can produce significant improvements in the restoration of facial fat thickness. It was effective in achieving aesthetic correction of the cheeks and provided durable improvement for most patients for at least 1 year. Although some patients had palpable lumps following treatment, there were no serious adverse effects and no treatment interruptions because of side effects. A hyaluronic acid product with larger particles appears to be a useful supplement to fillers for HIV-infected patients in need of treatment for facial lipoatrophy.

Acknowledgements

The study was supported by unrestricted research grants from BMS (Oslo, Norway) and Abbott (Oslo, Norway). The authors also wish to thank Q-Medical AB (Uppsala, Sweden) for a discount on the first order of SubQ.

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